# REMARKS

Restriction Requirement

The Office Action sets forth a 24-way restriction requirement. According to the Examiner, the inventions 1-24 lack a single inventive concept due to:

> A same or corresponding technical feature shared among inventions 1 and 3-24 is a polypeptide comprising a first portion of a split intein, a second portion of a split intein, and a target peptide interposed between the first portion of a split intein and the second portion of a split intein. However, this technical feature has already been taught by Holford et al. (Structure. 1998 Aug 15;6(8):951-6.) [this reference is cited in the PCT International Search Report of PCT/US99/30162 and is not attached to the instant Office Action].
>
> Holford et al. teach the concept of how head-to-tail cyclized recombinant peptides and proteins could be made using the taught Expressed Protein Ligation (EPL), where introduction of an N-terminal cysteine and a C-terminal thioester within the same polypeptide chain allows for intramolecular native chemical ligation; and that this process has been used to prepare synthetic circular protein domain (see entire document, especially p. 955, penultimate paragraph).
>
> *The specification defines the word "intein" is a polypeptide sequence that can catalyze a splicing reaction during post-translational processing of a protein (see p. 13, lines 3-5). Thus, when the teachings Holford et al. are read in view of this definition of "intein", the N-terminal polypeptide sequence of the recombinant protein containing the introduced N-terminal cycteine is deemed to be the first portion of a split intein; the C-terminal polypeptide sequence containing the introduced C-terminal thioester is deemed to be the second portion of a split intein; and the polypeptide sequence in between is deemed to be the target peptide that is to be cyclized.*
>
> Thus, the technical feature is not special since it was known in the prior art and therefore cannot make a contribution over the prior art. (italics for emphasis only)

Applicants select Group I claims 1-11, 14-40, and 53-89, drawn to a non-naturally occurring nucleic acid molecule encoding a polypeptide comprising a first portion of a split intein, a second portion of a split intein, and a target peptide interposed between the first portion of a split intein and the second portion of a split intein; an expression vector comprising said nucleic acid; a host system comprising said nucleic acid; method for making a peptide molecule with traverse. For reasons explained below, Applicants respectfully point out that the basis of the restriction based on Holford as noted above is erroneous.

The error relates to the equation of the modifications disclosed in Holford with the present claimed invention, due to a misreading of the definition of "intein". Applicants' specification, on page 12, lines 22-24 through to page 13, lines 1-2, recites the following:

> As used herein, the word "intein" means a naturally-occurring or artificially-constructed polypeptide sequence embedded within a precursor protein that can catalyze a splicing reaction during post-translation post-translation processing of the protein. A list of known inteins is published at http://www.neb.com/inteins.html. A "split intein" is an intein that has two or more separate components not fused to one another.

Thus, the single residue modifications of Holford do not disclose or suggest the present claimed invention. More specifically, the cyclization reaction disclosed by Holford is nothing more than an intramolecular peptide cyclization reaction involving a nucleophile at the N-terminus and a thioester at the C-terminus. Whether it works or not depends on the two ends finding one another. (See for example, Figure 1 in Holford et al.)

In contrast, in the claimed invention, the N-terminal intein is **not** the N-terminus of the peptide, nor is the C-terminal intein the C-terminus of a thioester. Applicants teach that the N- and C-terminal inteins are proteins that actually associate to form a complex that initiates and drives the cyclization reaction. (See for example, page 18, lines 5-23 through to page 2, lines 1-12 and figures 1 and 2). Within this complex the cyclization reaction occurs with the concomitant loss of the N- and C-terminal inteins. Although it is true that the nucleophile at the N-terminus is a thiol and the C-terminal has a thiolester, the high efficiency of the process is driven by the intein association.

Accordingly, Applicants respectfully request rejoinder of all claims as there is in fact a common technical feature among all claims. Examination of all claims is hereby requested on the merits. Although no fee is believed to be due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,

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